Semiquantitative assessment of iodine extravasation in acute ischemic stroke after mechanical thrombectomy

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Iodine extravasation is commonly seen in stroke patients after successful mechanical thrombectomy. Iodine extravasation may be associated with patient prognosis, and more iodine extravasation is highly associated with the development of severe hemorrhagic transformation (HT). Hence, it is essential to identify early hemorrhage after intra-artery therapy and the imaging indicators that can predict late hemorrhage transformation. Several studies have used different quantitative and non-quantitative methods to evaluate iodine extravasation. However, they concluded with different results.[1-3] The aim of our study was to propose two easy and practical semiquantitative methods to evaluate iodine extravasation and their relation to hemorrhage transformation.

The present study was approved by the Ethics Committee of People's Hospital of Deyang City (No. 2018-04-004, registration number: ChiCTR1800015971), and all participants gave informed consent. Ninety-three consecutive anterior circulation obstruction patients who underwent mechanical thrombectomy were enrolled in our study. The inclusion criteria for mechanical thrombectomy are as follows (1) stroke onset $\leq$6 h, (2) age $\geq$18 years old, (3) national institute of health stroke scale (NIHSS) $\geq$6, (4) Alberta Stroke Program Early Computed Tomography (CT) Score (ASPECTS) $\geq$6 and (5) no hemorrhage on CT. All patients underwent the dual-energy CT scan immediately after mechanical thrombectomy and follow-up conventional CT or MRI scan within 2 days. Further follow-up examinations were conducted according to the clinical status. We divided these patients into two groups depending on whether the patients had HT based on the results of dual-energy CT and follow-up examinations. Patients were excluded for the evaluation if they had any of the following situations: (1) a previous history of stroke (5/93), (2) failure with mechanical thrombectomy (9/93), (3) failure with image collection (6/93), and (4) other situations that cannot be included (one patient having posterior circulation hematoma immediately after mechanical thrombectomy).

Clinical data, including age, gender, baseline NIHSS, hypertension, diabetes mellitus, atrial fibrillation, cigarette smoking, onset to recanalization, and puncture to recanalization, were collected. The modified Rankin Scale (mRS) at 90 days was evaluated. Good clinical outcome was defined as mRS $\leq$2 at 90 days.

A dual-energy brain scan was obtained on third-generation dual-source CT (Somatom Definition FORCE; Siemens Healthcare, Forchheim, Germany). The dual-energy CT protocol was as follows: caudocranial scan direction, tube A/B: 80/150 kV tube voltage, mAs reference 310/207, 64×0.6 mm collimation on both detectors, 1.0 s rotation time, pitch 0.7, and iterative reconstructions with strength level of 3. The raw spiral data were reconstructed in three different series, virtual non-contrast image (VNC), iodine overlay map (IOM) images and a reconstructed 120 kV conventional CT (a mixed map of 80/150 kV image).

At first, the VNC and IOM images were used to identify whether the patients had iodine extravasation and/or hemorrhaging. For patients with iodine extravasation, we further used two semiquantitative methods to evaluate iodine extravasation. On the one hand, we evaluated the iodine extravasation areas using the modified Alberta Stroke Program Early CT Score (mASPECTS)[4] on reconstructed 120 kV conventional CT. Instead of evaluating the hypoattenuation areas with the ASPECTS, the mASPECTS was calculated by means of scoring the hyperattenuation areas with the ASPECTS method. For

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example, a patient without hyperattenuation areas would get a score of 10. On the contrary, a score of 0 indicates diffuse high density throughout the ASPECTS areas. On the other hand, we assessed the degree of iodine extravasation on the reconstructed 120 kV conventional CT by rating 0 and 1 (0 indicates the patients had no dense iodine extravasation, and 1 indicates the patients had dense iodine extravasation). We defined dense iodine extravasation as involving at least two ASPECTS areas and no normal brain tissues observed in the regions with extravasated iodine contrast when adjusting the appropriate window width and level. The mASPECTS and dense iodine extravasation were independently assessed by two readers. Interobserver agreement was calculated by weighted Kappa statistics with excellent agreement if $\kappa = 0.81-1.00$, good agreement if $\kappa = 0.61-0.80$, and less good or poor agreement if $\kappa < 0.60$. The mean mASPECTS values were obtained by the two readers for further analyses. The final score for dense iodine extravasation was assessed by two radiologists and disagreement would be resolved by a senior radiologist.

We used the European Cooperative Acute Stroke Study (ECASS) classification[5] to evaluate the type of hemorrhage. Two readers reviewed the follow-up examination results. Disagreements in readings were resolved by a senior radiologist. Brain hemorrhage was defined by the presence of persisting and/or increasing high-density parenchyma on follow-up CTs or low-intensity parenchyma in the T2-weighted image upon follow-up MRI.

Student's t test (for continuous variables with normal distribution), Mann-Whitney U test (for continuous variables with non-normal distribution), or χ^2/Fisher exact test was used to detect the difference between HT group and non-HT group. A univariate logistic regression analysis was used to evaluate the associations between clinical variables and imaging parameters, and hemorrhage transformation. Variables with $P < 0.1$ in the univariate analysis were entered into the multivariate model. The receiver operating characteristics (ROC) curve was used to evaluate the predictive value of the mASPECTS, dense iodine extravasation and their combination for predicting hemorrhage transformation. A P value less than 0.05 was considered statistically significant. The statistical analysis was performed with IBM SPSS Statistics version 22 (SPSS Inc, Chicago, IL, USA) and MedCalc Statistical Software version 19.0.7 (Medcalc Software bvba, Ostend, Belgium).

A total of 72 patients at People's Hospital of Deyang City from June 2018 to July 2019 were included in the final analysis. There were 29 stroke patients having early or late hemorrhage (HT group), and 43 patients without HT (non-HT group). The distribution of mRS scores at 90 days in the two groups is shown in Supplementary Figure 1, http://links.lww.com/CM9/A388. There were significant differences between the two groups in mRS scores (16.7% *vs*. 39.5%, $\chi^2 = 5.555$, $P = 0.018$), mASPECTS (5.0 [3.0, 6.0] *vs*. 9.0 [6.5, 10.0], $Z = 4.830$, $P < 0.001$) and the sign of dense iodine extravasation (87.5% *vs*. 11.6%, $\chi^2 = 27.738$, $P < 0.001$). Meanwhile, there were no significant differences in age, gender, onset to recanalization, puncture to recanalization, baseline NIHSS score, hypertension, cigarette smoking, diabetes mellitus, and atrial fibrillation (all $P > 0.05$) [Supplementary Table 1, http://links.lww.com/CM9/A388]. The Kappa analysis demonstrated good interobserver agreement with $\kappa = 0.800$ (95% CI, 0.742–0.856) and 0.845 (95% CI, 0.716–0.975) for the mASPECTS score and dense iodine extravasation, respectively.

There were 27 (37.5%) patients who had hemorrhage on follow-up examinations. Only 2 (2.8%) patients had hemorrhage on the VNC images. Among these patients, 23 of the 29 (79.3%) patients had scores of mASPECTS $\leq$6 and 21 of the 29 (72.4%) patients had dense iodine extravasation [Supplementary Table 2, http://links.lww.com/CM9/A388]. Representative cases of parenchymal hemorrhage are shown in Supplementary Figure 2, http://links.lww.com/CM9/A388.

The univariate logistic regression results were shown in Table 1. The multivariate logistic regression analysis showed that dense iodine extravasation (odds ratio: 5.511, 95% CI: 1.255–24.211, $P = 0.024$) was significantly associated with hemorrhage transformation.

Table 1: Univariate and multivariate analysis of the prognostic factors for hemorrhage transformation.

	Univariate analysis		Multivariate analysis	
Variables	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Age	0.998 (0.946–1.030)	0.546		
Gender	0.614 (0.237–1.589)	0.315		
Onset to recanalization	0.999 (0.994–1.004)	0.762		
Puncture to recanalization	0.988 (0.970–1.007)	0.213		
Baseline NIHSS score	0.938 (0.859–1.024)	0.151		
Hypertension	1.329 (0.495–3.567)	0.572		
Cigarette smoking	0.995 (0.926–1.070)	0.893		
Diabetes mellitus	1.875 (0.453–7.766)	0.386		
Atrial fibrillation	2.462 (0.855–7.090)	0.095	2.650 (0.735–9.550)	0.136
mASPECTS	1.578 (1.271–1.961)	<0.001	1.231 (0.953–1.590)	0.111
Dense iodine extravasation	11.484 (3.749–35.177)	<0.001	5.511 (1.255–24.211)	0.024

CI: Confidence interval; mASPECTS: Modified Alberta Stroke Program Early Computed Tomography Score; NIHSS: National Institute of Health Stroke Scale; OR: Odds ratio.

The ROC curve analysis of mASPECTS, dense iodine extravasation and their combination as predictors of hemorrhage transformation is shown in Supplementary Figure 3, http://links.lww.com/CM9/A388. The areas under the curves (AUCs) of the mASPECTS, score for dense iodine extravasation and their combination were 0.833 (95% CI, 0.726–0.910), 0.839 (95% CI, 0.733–0.915) and 0.850 (95% CI, 0.746–0.923), respectively. The cut-off for mASPECTS was 6, which showed a sensitivity of 75.86% and a specificity of 81.40%. The sign of dense iodine extravasation in stroke patients for predicting hemorrhage showed a sensitivity of 72.41% and a specificity of 88.37%. And the combination of two CT indicators for predicting hemorrhage showed a sensitivity of 79.31% and a specificity of 83.72%.

Our study used semiquantitative methods to assess iodine extravasation in acute ischemic stroke after successful mechanical thrombectomy. First, we found that an mASPECTS less than or equal to 6 was associated with hemorrhage transformation in the univariate analysis. The mASPECTS is a simple and clear method for observers to identify the high-density regions on simulated conventional CT. In addition, the interobserver agreement was good when assessing the mASPECTS. Studies have shown that widespread damage to the blood brain barrier (BBB) after endovascular therapy will occur secondary to the reperfusion injury, which may account for more brain regions having iodine extravasation. This finding was also supported by a previous study using the ASPECTS to predict prognosis that found the ASPECTS to be a simple and reliable indicator associated with patients' functional outcome and symptomatic intracerebral hemorrhage.[4] Second, we found that the sign of dense iodine extravasation in the local area was highly associated with hemorrhagic transformation with a high specificity of 88.37%. The interobserver agreement was very good on evaluating this sign. The proposed sign of dense iodine extravasation of the present study corresponds with the moderate or severe hyperdense intraparenchyma defined in the study by Shi *et al*.[6] They found that moderate BBB disruption was strongly associated with intracranial hemorrhage and poor outcomes. Compared with the subjective evaluation of the previous study, the semiquantitative method used by our work is more concise and practicable. The underlying pathophysiology mechanism might be due to locally severe disruption of BBB and basal lamina.[7] Hence, the regional, dense extravasated contrast areas would develop into delayed, severe hemorrhage.

In conclusion, for large anterior artery occlusion stroke patients after successful mechanical thrombectomy, patients with an mASPECTS $\leq$ 6 and/or a positive sign of dense iodine extravasation are prone to develop hemorrhaging, which is associated with poor outcomes. These two methods are based on evaluating simulated conventional CT reconstructed by dual-energy CT, and they might be used on conventional single-energy CT as well.

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Conflicts of interest

None.

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